



New Therapies for Alcohol Dependence Open Options for Office-Based Treatment

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AS EVIDENCE GROWS TO SUPPORT the combined use of medication and psychosocial intervention to help individuals with alcohol dependence, treatment of alcohol use disorders is increasingly shifting to the primary care office setting.

The US Food and Drug Administration (FDA) has approved 3 medications for the treatment of alcohol dependence: disulfiram, acamprosate, and naltrexone (the latter in both daily oral and monthly injectable formulations). The availability of these drugs, along with mounting evidence of their effectiveness when coupled with brief behavioral interventions, is making office-based care more feasible.

"Our thinking about treatment is evolving," said Mark Willenbring, MD, director of the Division of Treatment and Recovery Research at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). He explained that alcohol treatment is moving from almost exclusively specialist care to primary care with referrals to specialists for patients with more complex needs. The shift is similar to the one that has occurred in the treatment of depression, he said.

The vast majority of individuals with alcohol dependence in the United States receive no treatment, even though the disorder is second only to depression as the most common cause of disability, Willenbring said. The most commonly available treatment programs are based on a model developed in the 1970s, which emphasizes inpatient group counseling followed by referral to a community-based support group.

However, access to this model of care is limited by a lack of insurance coverage, the absence of treatment centers in many communities, the inability of some individuals to commit to immediate abstinence, and the stigma



Medications coupled with brief behavioral interventions are facilitating office-based treatment of alcohol dependence.

associated with such programs, Willenbring said.

Additionally, scientists have begun to recognize the heterogeneity of alcohol use disorders. Willenbring explained that most of the research on these disorders is based on studies of severely dependent individuals entering inpatient rehabilitation programs at middle age. But more recent research, focused on community-based samples, has identified a great range in severity of illness and a variety of presentations.

One such study is the National Epidemiologic Survey on Alcohol and Related Conditions, a survey of a nationally representative sample of more than 40 000 US individuals. Results from the first wave of the study, conducted in

2001-2002, indicate that alcohol disorders disproportionately affect the young and that they comprise 5 distinct subgroups, some of which include highly functioning individuals (Moss HB et al. *Drug Alcohol Depend*. 2007;91[2-3]:149-158).

TARGETING MEDICATIONS

Given that each of the currently available FDA-approved drugs has a different mechanism of action, it is possible that each may be best suited to certain subgroups of patients.

A recent review of the literature on medications for alcoholism identified a few such potential correlations (Johnson BA. *Biochem Pharmacol*. doi: 10.1016/j.bcp.2007.08.005 [published online ahead of print August 9, 2007]). For instance, oral naltrexone, which targets the μ -opioid system, appears to offer the most benefit to patients with a family history of alcohol problems and patients with strong cravings for alcohol. Disulfiram, an aversive agent that inhibits aldehyde dehydrogenase and causes unpleasant effects when alcohol is consumed, primarily benefits patients who are highly compliant or receive medication under supervision. Finally, acamprosate, which targets the brain's glutamate system, has been shown in European studies to benefit patients being treated for alcohol dependence; US studies, however, have found little efficacy. The reason for these contradictory results is unclear, and some scientists hypothesize that they may reflect differences in the types of patients included in the European and US studies.

A monthly injectable formulation of naltrexone, approved by the FDA in



April 2006, was developed to improve patient adherence and circumvent some adverse effects associated with oral naltrexone. Oral naltrexone must be taken daily, and some patients taking the drug experience nausea and other adverse effects. These 2 factors may lead to non-adherence and ultimately treatment failure. Although no studies have yet compared the 2 formulations directly, the data so far suggest high adherence rates with the monthly injectable formulation, with 1 study finding that 64% of participants received all 6 injections in the treatment protocol (Garbutt JC et al. *JAMA*. 2005;293[13]:1617-1625). Similar adverse effects have been reported for both formulations, but a head-to-head comparison will be necessary to determine if the severity of adverse effects differs, said Stephanie S. O'Malley, PhD, professor of psychiatry at Yale University School of Medicine, in New Haven, Conn.

O'Malley and colleagues recently published a randomized controlled trial of 82 patients who, after 4 days of abstinence, received either monthly extended-release (injectable) naltrexone or placebo (O'Malley SS et al. *J Clin Psychopharmacol*. 2007;27[5]:507-512). They found that this subgroup of patients did benefit from the treatment, with 32% remaining abstinent for the entire 6-month duration of the treatment period compared with just 11% of controls. Treatment also reduced heavy drinking days and the number of drinking days per month. Additionally, the researchers found a dose-response effect; patients taking 380 mg of extended-release naltrexone had a better response than did patients taking 190 mg.

The label for the extended-release formulation of naltrexone recommends that patients abstain from alcohol before beginning the drug, but does not specify for how long, O'Malley said. Previous studies had looked at patients abstinent for 7 days. But O'Malley noted that it may be difficult for many patients to remain abstinent for that long without assistance, particularly through a weekend, and that patients

who require inpatient detoxification generally stay for 4 days.

Given these factors, finding that only 4 days of abstinence before starting the drug is sufficient to achieve prolonged abstinence and reduce heavy drinking makes office-based use of extended-release naltrexone easier, O'Malley said. Before such medications were available, "physicians felt ill-equipped to treat alcohol-dependent patients and referred them out for specialty care," she said. "With these new tools, office-based treatment has the potential to greatly expand patient access to effective therapy for alcohol dependence."

NEW OPTIONS

A recent randomized controlled trial identified topiramate, a drug approved by the FDA to treat epilepsy and to prevent migraine headaches, as another potentially useful treatment for alcohol dependence (Johnson BA et al. *JAMA*. 2007;298[14]:1641-1651). The 14-week study included 371 individuals and found that topiramate reduced the proportion of heavy drinking days from baseline by 8.44 percentage points more than placebo.

Bankole A. Johnson, DSc, MD, PhD, who led the trial, hypothesizes that topiramate uses 2 different mechanisms to reduce the reinforcing release of dopamine that dependent individuals experience when they drink. Specifically, the drug reduces glutamate activity and boosts the inhibitory effects of γ -aminobutyric acid. Additionally, topiramate helps to normalize the activity of calcium channels in the brain in individuals whose alcohol use has caused perturbations in this system. Johnson, of the University of Virginia in Charlottesville, said that because alcohol dependence affects many brain systems, a drug that targets multiple systems may be preferable.

"It is exquisitely well-suited for office-based care," said Johnson, noting that a patient in crisis can take the drug immediately because a period of abstinence before starting treatment is unnecessary.

Willenbring said primary care physicians also may be more comfortable using topiramate because they already use it to treat seizure disorders. He noted that some physicians are already using the drug off-label to treat alcohol dependence and that he found that to be reasonable.

Like naltrexone and disulfiram, topiramate also appears best suited for a particular subgroup of individuals, those with chronic severe alcohol dependence, Johnson said. Additionally, he noted that physicians should titrate the drug very slowly to reduce adverse events. He explained that his team found a higher rate of adverse events in the trial than they typically observe in practice; however, they also titrated the drug faster in the trial. Among the adverse events noted in the trial were tingling or numbness (50.8% of patients taking topiramate vs 10.6% of controls), taste perversion (23% vs 4.8%), anorexia (19.7% vs 6.9%), and difficulty concentrating (14.8% vs 3.2%).

Willenbring said that these drugs represent the first generation of medications for alcohol dependence and he expects the next generation soon. He also noted that brief psychosocial interventions are a key part of successful treatment using the available drugs. These interventions, which require about the same level of support as behavior interventions commonly offered to patients with depression and diabetes, can be administered by a nurse, he said.

He recommended that physicians consult the NIAAA's recently updated *Helping Patients Who Drink Too Much: A Clinician's Guide* (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm). The guide outlines tools for rapid screening, assessment, and management of high-risk alcohol use, including medication use. He also stressed the importance of following up and emphasizing medication adherence.

"There are treatments for alcoholism, and the treatments do work," Johnson said. "More people need to be aware that there is something they can ask their doctor for." □